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Effect of Palmitoylethanolamide on inner retinal function in stable glaucoma patients. A prospective, randomized, single blind, crossover clinical trial by pattern electroretinogram.

(PEA2015)

Argomento: glaucoma therapy

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1 Rational

Glaucoma is a progressive and multifactorial neurodegeneration involving retinal ganglion cells (RGC) with their axons. Currently, the only approach proven to be efficient in preserving visual function is lowering intraocular pressure (IOP) both at initial and in advanced stages (1-4). Other possible treatment areas have been investigated, including ocular blood flow and neuroprotection.

There are experimental and population based studies indicating that perfusion pressure may be relevant in glaucoma but very difficult to measure (5).

As stated this year by the European Glaucoma Society guidelines (6), neuroprotection can be defined as a “therapeutic approach” aiming to directly prevent, hinder and, in some cases, reverse neuronal cell damage. Since glaucoma patients can continue deteriorating in spite of an apparent well controlled IOP, the need for effective non-IOP related treatments is widely acknowledged. Several compounds have been shown to be neuroprotective in animal models of experimental glaucoma, such as memantine (7) and brimonidine (8): but so far, no compound has reached a sufficient level of evidence to be considered as a neuroprotectant in humans.

Previous studies have demonstrated that damage to RGC occurs as a primary insult followed by a subsequent cascade of events leading to a secondary, slower, progressive injury whose final result is RGC death by apoptosis; even optic nerve head blood flow abnormalities may initiate this cascade (9, 10). Gupta in 2006 reported that secondary trans-synaptic degeneration may also involve higher visual centers (11).

Therefore, although IOP lowering is the major strategy for treatment of glaucoma, it is not always effective and enough to avoid glaucoma progression. Neuroprotection can be considered an additional therapeutic strategy targeting RGCs and neurons of higher visual centers (12).

Palmitoylethanolamide (PEA) is categorized as an endocannabinoid-like molecule, it is now available as tablet (Visimast[®] 600 and 300 mg) and as eye drops (Defluxa[®]). It has been demonstrated to have at least three (some) potential beneficial effects in glaucoma patients.

In fact, the administration of PEA enhances aqueous humor outflow facility: this effect appears to be mediated at least partially by a SR144528-sensitive, non-CB1/CB2 receptor, the GPR55 receptor, and the PPAR α receptor, and involves p42/44 MAPK pathway. This property provide mechanistic basis for the potential of PEA as a new therapeutic agent for the treatment of elevated IOP (13). Some clinical studies have detected a significant IOP lowering effect of oral assumption of PEA 600 mg (14, 15).

Moreover, it is able to exert direct vasorelaxation of the (bovine) ophthalmic artery in a time-dependent manner via the transcription factors PPAR α suggesting a function for them in the physiological mechanisms of vascular regulation (16, 17). The vasorelaxant role of endocannabinoids raises the supply of oxygen to the retina and could prevent ischemic injury.

Finally, some studies have pointed out the role of PEA in affording protection against neurotoxic damage of central nervous system and eye. In vivo (on rat retina) studies have demonstrated that PEA protects against ganglion cell death by activation of cannabinoids receptors (CB1 and TRPV1) modulating the glutamate-excitotoxicity and therefore altering the course of apoptosis (18, 19).

Todate, endocannabinoids constitute the newest of the neuromodulators that are found in neural and non-neural tissues throughout the body. About retina, there is general agreement that

cannabinoids suppress dopamine release and presynaptically reduce transmitter release from cones and bipolar cells (19).

1 Study objectives

Our general purpose is to evaluate the potential beneficial effects of PEA 600 mg supplementation on RGCs function in subjects with glaucoma (20) by pattern electroretinogram.

1.1 Primary objective

To assess effects of PEA 600 mg a tablet a day on PERG examination at three months of therapy.

1.2 Secondary objectives

To assess effects of PEA 600 mg on IOP values, if any.

To record visual acuity, visual field, HRT, CCT, GDx and OCT (GCC) changes, if any.

To follow QL perception (GV and GH of NEI VFQ25)

2 Study design and planning

Monocentric, randomized, prospective, single blind, two treatment and two period crossover study.

We have proposed a cross-over trial to avoid or to detect the bias due to intraindividual variability and because, from our preliminary observation, we have noted that the effects of PEA on PERG are completely reversible after withdrawal, within one month.

We didn't considered a placebo treated group because the patient cannot interfere with the PERG measurement that is objective and totally patient-independent.

2.1 Center

Clinica Oculistica IRCCS Policlinico San Matteo Foundation, Pavia

2.2 Study duration

Study duration 12 months

Enrolment period 6 months

Minimum Follow-up 6 months

Start: January, 2015; end January, 2016

Total sample size: 40 patients

3 Subjects

3.1 Eligibility criteria

Eligibility criteria will be as follows:

-age 18 years or older

-diagnosis of primary OAG (POAG) (see Definitions);

-controlled IOP (<18 mmHg, morning value) with any topical lowering medication (beta-blockers, carbonic anhydrase inhibitors, alpha2agonists, prostaglandine analogues as monotherapy or as

associative therapy; betablocker/carbonic anhydrase inhibitor, betablocker/alpha2agonist, prostaglandine/betablocker and alpha2agonist/carbonic anhydrase inhibitor fixed combinations as monotherapy or in association);

- stable IOP<18 mmHg in the last 2 years

- stable disease in the last 2 years (no more than -1 dB/year at MD of visual field)

- at least two reliable visual fields per year in the last 2 years

- no filtering surgery or other ocular surgery in the preceding 6 months

- written consent to participate to study procedures (see Detailed study procedures) and data utilization in an anonymous form

Exclusion criteria.

- ocular hypertension with normal optic nerve and visual field

- contraindication to PEA

- glaucomatous scotomas within 10 degree from fixation

- any condition limiting the patient's ability to participate in the study;

- other causes of visual field changes, such as cataract, myopic corioretinopathy, macular diseases, retinal vascular occlusion;

3.2 Withdrawal criteria

Withdrawal criteria: patients not wishing to participate any longer after signing informed consent or any other condition that, upon clinical judgment of the investigator, will make unacceptable further study participation for that individual patient.

4 Treatments currently available in the clinical practice

The treatment of glaucoma is based on IOP-lowering medication prescription. It is well known that IOP is not to be the only risk factor for developing or progressing the disease, but todate there is low evidence of others systemic therapies on humans.

5 Detailed study procedures

5.1 Screening procedures

The inclusion/exclusion criteria were verified after careful examination of patients' medical charts. If eligible, at his/her first clinical visit after study start the patient will be informed of the protocol and his/her consent required in written form, for the use of their clinical data for scientific evaluations.

5.2 Planned assessments

Baseline. After enrolment, all patients will undergo the following routine procedures:

- complete ophthalmic examination

 - Visual acuity (VA)

 - Anterior segment evaluation (anterior chamber, lens and angle)

IOP (Goldmann tonometry)

pachimetry (pachette 2 pachimeter) measurement

optic nerve evaluation with indirect lens (Volk 90)

optic nerve and retinal fiber evaluation with OCT study, HRT and GDX

pattern electroretinogram (PERG)

visual field examination (Humphrey 24-2 sita- standard): Mean Deviation (MD), Pattern Standard Deviation (PSD), Glaucoma Hemifield Test (GHT), Visual Field Index

quality of life evaluation by general vision and general health scales of the NEI VFQ 25.

Patients will be randomized to group A (PEA 600 mg one tablet a day) or to group B (current topical therapy) for 3 months and subsequent visit will be scheduled.

At *visit 1* (V1, month 3) all patients will be submitted to the following routine procedures:

complete ophthalmic examination

Visual acuity (VA)

Anterior segment evaluation (anterior chamber, lens and angle)

IOP (Goldmann tonometry)

pachimetry (pachette 2 pachimeter) measurement

optic nerve evaluation with indirect lens (Volk 90)

optic nerve and retinal fiber evaluation with OCT study, HRT and GDX

pattern electroretinogram (PERG)

visual field examination (Humphrey 24-2 sita- standard)

quality of life evaluation by general vision and general health scales of the NEI VFQ 25

Patients will be crossed-over: patients of group A will be unprescribed tablets, and group B will assume PEA 600 mg, one tablet a day, for 3 months.

Visit 2 (V2, month 6). All patients will be submitted to the following routine procedures:

complete ophthalmic examination

Visual acuity (VA)

Anterior segment evaluation (anterior chamber, lens and angle)

IOP (Goldmann tonometry)

pachimetry (pachette 2 pachimeter) measurement

optic nerve evaluation with indirect lens (Volk 90)

optic nerve and retinal fiber evaluation with OCT study, HRT and GDX

pattern electroretinogram (PERG)

visual field examination (Humphrey 24-2 sita- standard)

quality of life evaluation by general vision and general health scales of the NEI VFQ 25

Other variables

Other variables that will be collected for each subject at baseline/over time will be: date of birth (month/year) and sex, the following information will be collected: therapy (systemic and topical), medical history (systemic and ocular, ie previous lasers/surgery).

6 Study definitions and diagnostic criteria

6.1 Glaucoma diagnosis

The diagnosis of glaucoma will require: IOP >21 mmHg on at least two consecutive visits at the time of first diagnosis, presence of glaucomatous optic nerve head (ONH) confirmed by an expert fundus examination and at least three reliable Humphrey 24-2 full threshold visual field tests performed on different days showing a glaucomatous or suspected glaucomatous defect.

It will be performed (or confirmed, if the patient is being referred from another centre) by a senior ophthalmologist working at the Eye Clinic of the Fondazione.

6.2 Ocular examination

Visual Acuity determined in Decimals unit.

Slit lamp examination of the anterior and posterior segment with particular attention to the retina and the optic nerve aspect.

IOP measurement (Goldmann tonometry). The MD who will measure IOP is blinded to study procedures.

6.3 HRT and Gdx

HRT is a non-invasive procedure that scans the eye. The HRT takes 3-dimensional photographs of the optic nerve and retina using a special laser. It starts by photographing the surface of the optic nerve and then focuses on deeper and deeper layers before putting them all together to create the 3-dimensional image. These photographs can be used to evaluate optic, disc, retinal nerve fiber layer and retina.

The GDx nerve fiber analyzers measure the retinal nerve fiber layer (RNFL) thickness with a scanning laser polarimeter based on the birefringent properties of the RNFL. Measurement is obtained from a band 1.75 disc diameters concentric to the disc. It projects a polarized beam of a light into the eye. As this light passes through the NFL tissue, it changes and slow. The detectors measure the change and convert it into thickness units that are graphically displayed. The GDx measure modulation around an ellipse just outside the optics disc and ratios of the thickest points either superiorly or inferiorly to the temporal or nasal regions.

6.4 Visual field examination

The Humphrey Visual Field is a special automated procedure used to perform perimetry, a test that measures the entire area of peripheral vision that can be seen while the eye is focused on a central point. During this test, lights of varying intensities appear in different parts of the visual field while the patient's eye is focused on a certain spot. The perception of these lights is charted and then compared to results of a healthy eye at the same age of the patient in order to determine if any damage has occurred. This procedure is performed quickly and easily in about 15 minutes, and is effective in diagnosing and monitoring the progress of glaucoma. Main parameters to evaluate damage and progression or not are: mean defect and pattern standard deviation (MD and PSD, decibels), Glaucoma hemifield test (GHT, qualitative description of the examination defined

normal, borderline, outside normal limits), and the visual field index (VFI, a global index that assigns a number between 1% and 100% based on an aggregate percentage of visual function with 100% being a perfect age-adjusted visual field).

6.5 Optical coherence tomography (OCT)

Optical coherence tomography is an established medical imaging technique. It is widely used to obtain high-resolution images of the anterior segment of the eye and the retina, which can provide a straightforward method of assessing axonal integrity in Glaucoma being useful in follow-up examination to detect glaucoma progression.

6.6 Pattern Electrophoretogram (PERG)

The PERG is an objective and direct measure of inner retinal function being correlated with RGCs activity (21, 22), which has been found to document and predict early glaucomatous changes. There is also an indication that PERG may document, at pre-clinical stage, an improvement of RGCs function following therapeutic IOP reduction (23). therefore PERG can be considered as an early indicator of functional RGC changes following an intervention aimed at counteracting apoptosis. PERG measures the function of the retina: when light from an image enters the eye, it is converted into electrical energy by specialized cells in the retina. These cells send electrical impulses through the optic nerve to the brain where the image is processed. The ERG test records how well the cells of the retina are conveying electrical impulses within the eye. In particular the p50 wave reflects the ganglion cells vitality/activity.

6.7 NEI VFQ 25 item

The patients' quality of life will be examined with the Italian version of the 25 item National Eye Institute Visual Function Questionnaire (24). The 25 item NEI-VFQ is a vision-targeted non-disease-specific instrument designed to measure the impact of some ocular disorders on vision related quality of life. Depending on the item, responses to this questionnaire pertain to the frequency or severity of a symptom or a problem with the functioning. The NEI-VFQ scores can range from 0 to 100 with lower scores indicating more problems or symptoms.

6.8 Single blind procedures

All the involved personal performing visual field examination, optic nerve evaluation, IOP measurement and PERG test will be blinded to patient's treatment period; also who will analyse the data will be blind to the treatment group.

6.9 Adverse events

Systemic and topical adverse events will be collected.

Methods for assessing and recording: patients will be asked at each visit about therapy's comfort and side effects.

For each AE the following information will be recorded in the patient's medical chart:

- nature of adverse event
- date and time of occurrence and disappearance (i.e. duration)
- intensity: mild, moderate or severe
- frequency: once, continuous or intermittent
- decision regarding study: continuation or withdrawal
- relation to the study medication

- measures undertaken to treat it

AEs will be treated according to the usual clinical practice. In the event of a serious adverse event the drug will be discontinued.

7 Description of study supplement

See Annexes (technical description)

8 Statistical issues

8.1 Elements for sample size calculations or study power

From our preliminary observation we noted that the mean difference in amplitude p50 between baseline and 3-month values was 0.7 microVolt (SD 0.7), in particular from a mean of 1.4 to a mean of 2.1. A two-sided t-test paired achieves 87% power to infer that the mean amplitude at baseline is 1.4 when the total sample size of a 2x2 cross-over design is 40, the mean amplitude after 3 months of treatment is 2.1, the standard deviation of the period differences for each subject within each sequence is 0.7, and the significance level is 0.05.

8.2 Analysis plan primary objective

For the primary analysis, a Anova two-sided test (or equivalent non parametric test) will be used to compare difference between period of treatment.

8.3 Analysis plan secondary objectives

Descriptive statistics will be obtained for all variables assessed in the study population. Mean and standard deviation will be used for normally distributed variables, mean and interquartile range for skewed distributions, proportions for categorical variables.

For group comparisons, Student paired t test (Wilcoxon test for skewed distributions) will be used for quantitative variables (ANOVA for repeated measure or Friedman for >2 groups respectively), and McNemar test for categorical variables. In all cases, two-tailed tests will be applied. P-value <0.05 will be considered significant. Whenever relevant, 95% confidence intervals (95%CI) will be calculated.

Logarithmic transformation will be applied to skewed variables, whenever relevant to achieve normality.

Linear regression models for repeated measures will be used to take into account both eyes per patients and trends over time of the ophthalmological in the planned groups/subgroups comparisons.

9 Data management and confidentiality issues

All study material (protocol, CRF, completed CRF, administrative documents) will be maintained in a safe (closed room) place site in the Glaucoma center of the Clinica Oculistica for 5 years.

9.1 Patient's lists

The following lists will be maintained:

Enrolled patients (code-date written consent)

Patient's code identification log (name-surname, month-year of birth, date written consent, code)

9.2 Data recording

A standard case report form (CRF) has been designed, to record in written all study details, and will be completed by the designated personnel. Once completed, CRF will be signed by PI and maintained in the patient's clinical chart.

Corrections will be dated, signed and justified by PI or designated personnel.

In the patient's medical records, study participation, date of consent, assigned code and any other relevant information will be recorded.

All data in the CRF will be checked for completeness, coherence, and conformity to the protocol. Missing data will be searched for in the medical charts on a regular basis.

10 Ethical issues

The study will be conducted according to recommendations of the Helsinki declaration (revision 2000, Edimbourg) and to the Italian Good Clinical Practice legislation (DM 15 Luglio 1997 and modifications).

10.1 Informed consent

To be included in the study the written consent to participate the study procedures is necessary. Patients not wishing to participate any longer after signing informed consent will withdrawal consent whenever he likes.

The aim and the procedures of the study will be explained to patients during a routine follow-up visit, with an individual speech of about half an hour. The doctor will explain also how to adhere, the chance not to adhere or to adhere and withdrawal without any consequence on care quality. Patients will be given time for questions and to decide if adhere or not to the study.

10.2 Consent withdrawal

Each patient not wishing to participate any longer after signing informed consent can withdraw its consent; if the doctor will note any adverse event, the therapy will be stopped.

10.3 Insurance

An insurance is activated at the Fondazione IRCCS Policlinico San Matteo, to cover any damage due to the clinical study.

10.4 Potential conflicts of interest

All the researchers participating to the study declare that they have no potential conflict of interest.

10.5 Other ethical issues

The study design is not complex, does not interfere with routine clinical management and does not require additional human resources in the participating centre.

11 Costs and financing

Medivis will supply all tablets needed for all the 40 patients for the three months of treatment.

12 **Staff and duties**

12.1 **Fondazione IRCCS Policlinico San Matteo**

Unità Operativa	Nominativo	Ruolo
Clinica Oculistica	Gemma Caterina Maria Rossi	Progettazione, Coordinamento, Arruolamento pazienti, raccolta dati
Clinica Oculistica	Marta Raimondi	Misurazione IOP (blinded)
Clinica Oculistica	Giulio Ruberto	Valutazione del PERG (blinded)
Clinica Oculistica	Patrizia Piccinini	Esecuzione PERG (blinded)
Direzione Scientifica	Carmine Tinelli, Luigia Scudeller	Analisi statistica (blinded)

13 **Data property, publications and further studies**

The proposing group will manage patients' data and publications. The manufacturers of the study drugs will not have access to the data, nor to the various drafts of the publication which is expected to be written.

The authors of the publications will be decided on the basis of indications contained in the Uniform Requirements for Manuscripts (http://www.icmje.org/urm_full.pdf).

Strategy of publication: the main manuscript resulting from this study will be submitted to an indexed journal.

Manuscript preparation will following the STROBE guideline: <http://www.equator-network.org/resource-centre/library-of-health-research-reporting/reporting-guidelines/>

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